

Genetic Testing for Long QT Syndrome



Assessment
Program
Volume 22, No. 9
February 2008

Executive Summary

Background

A genetic test is currently commercially available for mutations associated with the long QT syndrome (LQTS). The Romano-Ward syndrome (RWS), which is the most common type of LQTS and lacks noncardiac manifestations, can be difficult to diagnose by clinical methods. Genetic testing for RWS may improve the accuracy of the diagnostic work-up and lead to treatment that is efficacious at reducing the incidence of sudden death and/or other cardiovascular symptoms in affected patients.

Objective

Review evidence to determine if genetic testing for LQTS improves health outcomes for patients with known or suspected LQTS.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the terms “long QT syndrome” OR “LQTS,” cross-referenced with the terms “genetics” OR “gene” from 1990 through October 2007, limited to English-language articles on human subjects. Electronic search was supplemented with hand-search of relevant bibliographies.

Selection Criteria

Studies were selected that included primary data on patients with LQTS and relevant evidence on the diagnostic accuracy of clinical or genetic methods for LQTS; the differential prognosis of LQTS by specific syndrome and/or LQTS subtype; or the outcomes of treatment with beta-blocker medications or implantable cardioverter-defibrillator (ICD) therapy.

Main Results

The commercially available genetic test for LQTS is accurate in identifying a mutation that is present, and in excluding mutations that are not present. The diagnostic accuracy of genetic testing for detecting the clinical syndrome of LQTS cannot be determined with certainty due to the lack of a true gold standard for the clinical diagnosis. In patients with a known clinical diagnosis of LQTS, approximately 70% are found to have a deleterious mutation associated with LQTS, indicating that other genetic mutations may exist that have not been identified.

Of all patients found to have a genetic mutation, only a minority meet the clinical criteria for LQTS. Therefore, genetic testing will identify additional individuals with possible LQTS, compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have either the pathophysiologic channelopathy associated with LQTS or the true clinical syndrome of LQTS. It is possible to conclude that patients who are identified as genetic



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carriers of LQTS mutations have a non-negligible risk of adverse cardiac events, even in the absence of clinical signs and symptoms of the disorder.

Treatment with beta blockers is likely to reduce the rate of adverse cardiovascular outcomes, including sudden death. Beta-blocker therapy appears to be effective in reducing adverse outcomes both for patients diagnosed by clinical criteria and for patients diagnosed by genetic testing.

Genetic testing for LQTS can identify the specific syndrome present, and/or the subtype of Romano-Ward syndrome. However, the evidence is not sufficient to conclude that information on LQTS subtypes obtained from genetic testing leads to important changes in clinical management.

Author's Conclusions and Comments

There is no direct evidence that use of genetic testing for LQTS improves outcomes. Although there are limitations in the evidence on analytic validity, clinical validity, and clinical utility, nonetheless, the overall case that genetic testing will improve outcomes in selected patient populations is compelling. Conventionally, diagnosis of LQTS is based on clinical criteria. There is no gold standard for diagnosis; however, the Schwartz score has been commonly used. Two large (n>500) studies compared diagnostic performance of clinical criteria against genetic testing and genetic testing against clinical criteria, respectively. Both show that genetic testing will identify more individuals with a LQTS mutation compared to the number of patients diagnosed with LQTS by clinical methods. These findings are consistent with what is well known clinically: that there is substantial risk of underdiagnosing LQTS, with results that may be catastrophic.

Despite uncertainties in the diagnostic accuracy of genetic testing, the clinical utility of testing is high. This is due to the catastrophic outcomes associated with LQTS and the availability of low-risk treatments that are efficacious in reducing adverse outcomes. The risk of undertreatment of such individuals is therefore likely to far outweigh the risk of overtreatment of such individuals.

For individuals with a known LQTS mutation in the family but who do not themselves meet the clinical criteria for LQTS, genetic testing will improve outcomes. These individuals have a high pretest probability of disease and LQTS can be diagnosed with certainty if the test is positive. Treatment of these individuals with beta blockers will reduce the incidence of subsequent cardiovascular events. Furthermore, because the specific mutation is known prior to testing, the disease can be ruled out with certainty if results are negative.

For other patient populations, there may be a benefit as well. For patients who have some signs and symptoms of LQTS, but no known mutation in the family, testing may be beneficial. In this situation, LQTS can be diagnosed with reasonable certainty if a class I mutation is identified, however the likelihood of false-positive results is higher than if a known mutation was present in the family. In patients with lower pretest probabilities of disease, the utility of testing declines, although precise risk/benefit thresholds cannot be established. The table provides an overview of the potential benefit of genetic testing in the spectrum of clinical populations that are encountered in practice.

Genetic testing has not been demonstrated to improve the outcomes of those individuals who already meet clinical criteria for LQTS. Once diagnosed with LQTS, all patients should be treated with beta blocker therapy and lifestyle modifications. There is no evidence to suggest that genetic testing influences clinical decisions on whether or not to treat with an implantable cardioverter-defibrillator (ICD). While many experts consider LQT3 to be less responsive to therapy with beta blockers, studies that address this question differ in their results, with some indicating a similar response to beta blockers for LQT3 genotype and others indicating a lack of benefit. Therefore, it is not possible to conclude that genetic testing for LQTS improves outcomes when used to direct therapy or determine prognosis.

However, if individuals who meet the clinical criteria for LQTS have immediate family members with indications for genetic testing, genetic testing of the index patient (i.e., clinically diagnosed patient) can be instrumental in interpreting results of genetic testing for family members. If a

Table. Potential Patient Indications for Genetic Testing

	Meets Clinical Criteria for LQTS	Some Signs or Symptoms of LQTS; Does Not Meet Clinical Criteria	No Signs or Symptoms of LQTS
Family history positive and known mutation in family	– (?)	++	+
Family history positive but family mutation status unknown	– (?)	+	+
Family history negative	–	+ (?)	–

++ definite benefit of genetic testing

+ probable benefit of genetic testing

? uncertain benefit of genetic testing

– no benefit of genetic testing

Clinical criteria for LQTS – Schwartz score ≥ 4 (other definitions possible as well)

FH positive: family history positive for sudden death at age <30; or clinical diagnosis of LQTS in family (without known mutation)

Signs/symptoms LQTS: long QT interval on EKG; syncope; aborted cardiac arrest

known mutation is found in the index patient, then genetic testing of family members can be targeted and both positive and negative results can be interpreted with greater certainty. Therefore, the family member will benefit from genetic testing of the index patient.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether genetic testing for LQTS meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for LQTS, nor are any kits being actively manufactured and marketed for distribution. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. While the FDA has technical authority to regulate home-brew tests, there is currently no active oversight nor any known plans to begin such oversight. Home-brew tests may be developed using reagents prepared in-house or, if available, commercially manufactured analyte-specific reagents (ASRs). ASRs are single biological reagents “intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens” and must meet certain FDA criteria but are not subject to premarket review.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Although there are limitations in the evidence on analytic validity, clinical validity, and clinical utility, the overall case that genetic testing will improve outcomes in selected patient populations is compelling. For patients with a moderate-to-high pretest likelihood, the positive predictive value (PPV) of genetic testing will be high, and few patients will be misclassified as having LQTS when they do not. However, for patients with a low pretest likelihood of LQTS, the PPV of testing will be lower and the utility of testing less certain.

For determining prognosis and directing therapy, the evidence is sufficient to conclude that genetic testing offers some information on risk stratification above that provided by clinical evaluation. However, genetic testing has not identified subgroups of patients with risk low enough

to forego treatment, nor has testing identified subgroups with risk high enough to justify more aggressive treatment, such as prophylactic implantation of an ICD. Similarly, while there is some evidence that certain LQTS subtypes may respond differently to beta-blocker therapy, the evidence on this is not consistent and therefore, it is not possible to conclude that genetic testing to direct therapy improves outcomes.

3. The technology must improve the net health outcome.

For patients with a moderate-to-high pretest likelihood of LQTS, in whom the diagnosis cannot be made after clinical evaluation, genetic testing will improve health outcomes. In these individuals, genetic testing will correctly identify patients with LQTS who cannot be diagnosed by other methods, and lead to appropriate treatment.

Patients who are identified as having LQTS by purely genetic testing have a lower risk for cardiovascular events compared to patients with a clinical diagnosis. However, the risk of cardiovascular events and sudden death in patients identified by genetic testing remains high enough to warrant treatment with lifestyle modifications and beta-blocker therapy. Observational studies show a large decrease in the incidence of cardiovascular events reported after treatment with beta blockers.

For risk stratification, the evidence is not sufficient to conclude that health outcomes are improved. Although the evidence suggests that genetic testing will aid in risk stratification, there is no evidence to suggest that testing will lead to meaningful changes in clinical management that improve health outcomes.

4. The technology must be as beneficial as any established alternatives.

The alternative to the use of genetic testing for diagnosing LQTS is using clinical methods alone for diagnosis. As discussed above, clinical methods are insensitive compared to genetic testing. When used in the correct population with a moderate-to-high pretest probability of disease, genetic testing is more beneficial than diagnosis by clinical criteria alone.

For risk stratification, the use of genetic testing for LQTS has not been demonstrated to improve outcomes.

5. The improvement must be attainable outside the investigational settings.

At least one commercially available genetic test for LQTS is on the market, and can be ordered by any treating physician in the U.S. However, the interpretation of this test may be complex and require some expertise in genetics. Therefore, it is most appropriate that genetic testing be undertaken in clinical environments where expertise in genetic testing is available, and genetic counseling provided to patients in order to assist in complex clinical decision-making.

Based on the above, genetic testing for LQTS meets the TEC criteria for establishing the diagnosis of LQTS, in the following populations:

1. Individuals who do not meet the clinical criteria for LQTS, but who have:
 - a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation; or
 - a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable; or
 - signs and/or symptoms indicating a moderate to high pretest probability¹ of LQTS.

¹ Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2–5.

2. An individual who meets the clinical criteria for LQTS and who has a close relative at risk for LQTS with an indication for genetic testing. In this circumstance, testing of the individual with LQTS is intended to inform genetic testing options for at-risk relatives.

Genetic testing for LQTS does not meet the TEC criteria for determining prognosis and/or directing therapy in patients with known LQTS who do not have close relative(s) with indications for genetic testing.

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Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

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Assessment Objective

This Assessment reviews the available evidence to determine if genetic testing for long QT syndrome (LQTS) improves health outcomes for patients with known or suspected LQTS.

In the absence of direct evidence to answer the question of primary interest, we sought indirect evidence to establish a causal chain: that genetic testing improves the diagnosis of LQTS, resulting in changes in management that improve health outcomes. For prognostic use, the chain is that genetic testing provides additional information that results in patient management changes that improve health outcomes. As with TEC Assessments of other genetic tests, we apply the assessment framework recommended by EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Workgroup, an initiative of the National Office of Public Health Genomics at the Centers of Disease Control and Prevention. The EGAPP framework addresses analytic validity, clinical validity, and the clinical utility of a genetic test.

Background

Congenital Long QT Syndrome

Congenital LQTS is a conduction disorder of the heart in which a defect in repolarization of cardiac muscle leads to an increased likelihood of ventricular arrhythmias and sudden death. The incidence of the most common type of LQTS, Romano-Ward syndrome (RWS) is currently estimated to be 1 in 5,000, which is higher than previously believed (Ackerman 2005). The RWS is probably the most common etiology for sudden, unexplained death, i.e., sudden cardiac death in patients without evidence of heart disease prior to death or at autopsy (Behr et al. 2005; Ackerman 2005).

In the last two decades, advances in molecular genetics have led to a better understanding of the pathophysiologic mechanisms underlying LQTS. Basic research has established that LQTS is an inherited disorder of cardiac ion channels (Priori et al. 2001). Abnormal flow of cardiac ions across these channels leads to delayed repolarization of cardiac muscles, and prolongation of the QT interval observed on electrocardiogram (Marcus 2005). Abnormal depolarization leads to an increased risk for polymorphic ventricular tachycardia, especially torsades de pointes, a potentially lethal

arrhythmia that can degenerate into ventricular fibrillation and death (Chiang and Roden 2000).

Recent research has also established that LQTS is a heterogeneous disorder, with multiple types that may differ in clinical expression, risk of sudden death, and response to treatment (Collins and Van Hare 2006). Currently there are 4 recognized LQTS syndromes (Table 1). These are the Romano-Ward syndrome, Jervell and Lange-Nielsen syndrome, Andersen-Tawil syndrome, and Timothy syndrome. Some of these syndromes are associated with other congenital abnormalities (Collins and Van Hare 2006).

RWS is the most common form of LQTS, accounting for approximately 85% of all LQTS cases (Hofman et al. 2007). In this syndrome, abnormalities are confined to the heart and patients do not show signs of other congenital defects (Vincent 2005). This is the only LQTS syndrome that is not associated with extracardiac manifestations and, therefore, may be more difficult to detect clinically compared with other LQTS syndromes. Within RWS, there are at least 6 subtypes that are associated with variable clinical expression and result from mutations in 1 of 5 different genes (Table 2) (Collins and Van Hare 2006).

The Jervell and Lange-Nielsen subtype is associated with congenital deafness (Daley et al. 2007). The prolongation of the QT interval is more marked, usually longer than 500 msec, corresponding with a high risk for malignant ventricular arrhythmias and sudden death. Fifty percent of affected individuals experience a cardiac event before the age of 3 years, and more than half of untreated individuals die before the age of 15 years (Daley et al. 2007).

The Andersen-Tawil syndrome is associated with multiple organ involvement, including dysmorphic body features and periodic paralysis (Tawil and Venance 2007). This syndrome has a distinctive triad of periodic paralysis, ventricular arrhythmias, and a prolonged QT interval. Dysmorphic features include short stature, syndactyly and scoliosis (Tawil and Venance 2007). Individuals typically present during the first or second decades because of weakness and/or syncope. The Timothy syndrome is a multisystem disorder involving abnormalities of the skeleton, nervous system and the heart (Splawski et al. 2006). The QT interval is markedly prolonged, ranging between 480 and

Table 1. Clinical Features of Congenital Long QT Syndromes

Form of Congenital LQT	Typical Age at Onset	Presenting Signs and Symptoms	Arrhythmia Phenotype	Management
Romano-Ward Syndrome	Infancy through middle-age; most commonly pre-teens through 20s; later onset suggests phenotype 3	<ul style="list-style-type: none"> – Syncope without warning, cardiac arrest, sudden death risk, 4%—death is the first sign in about 10–15%. – Triggers (phenotype 1) exercise, emotion; (phenotype 2) exercise, sleep startle; (phenotype 3) sleep. 	<p>Cardiac: Ventricular tachycardia torsades de pointes, which may degenerate into ventricular fibrillation.</p> <p>Noncardiac: none</p>	<ul style="list-style-type: none"> – For LQT1 and LQT2 phenotypes, prophylactic beta blockers; – Pacemakers may be necessary for those with symptomatic bradycardia associated with beta-blocker therapy. – Automatic external defibrillators at home, school, and play areas suggested. Implantable cardioverter-defibrillators (ICDs) may be necessary for those with beta-blocker-resistant symptoms, inability to take beta blockers, history of cardiac arrest, and for people with LQT3 phenotype. – Avoid drugs that prolong the QT interval and activities known to precipitate syncopal events.
Andersen-Tawil Syndrome	First or second decade	<ul style="list-style-type: none"> – Periodic paralysis – Syncope – Palpitations 	<p>Cardiac: Bidirectional VT, polymorphic VT, multifocal premature ventricular contractions</p> <p>Noncardiac: Episodic flaccid muscle weakness, dysmorphic features</p>	<ul style="list-style-type: none"> – Oral potassium when serum potassium <3.0 mmol/L; IV calcium gluconate rarely needed. – Prophylactic Rx: lifestyle and dietary modification; carbonic anhydrase inhibitors, daily slow-release potassium, precautions with anesthetics. – Avoid drugs that prolong QT intervals.
Timothy Syndrome types 1 and 2 (type 2 extremely rare)	Infancy/childhood	<ul style="list-style-type: none"> – Syncope – High incidence of cardiac arrest/sudden death, usually during childhood 	<p>Cardiac: Very long QTc intervals (480 to 700 msec), AV block. Type 2, average age of death from ventricular tachycardia, 2.5 yrs (2 reported cases).</p> <p>Noncardiac: Unilateral or bilateral cutaneous syndactyly, immunodeficiency, hypoglycemia, cognitive disorders, autism, congenital heart defects, dysmorphic facial features.</p>	<ul style="list-style-type: none"> – ICD—high incidence of sudden death even with use of beta blockers and pacemaker therapy.
Jervell and Lange-Nielsen	Infancy hearing loss	<ul style="list-style-type: none"> – Deafness in child – Syncope during periods of stress, exercise, or fright. 	<p>Cardiac: Tachyarrhythmias, including ventricular tachycardia, episodes of torsades de pointes ventricular tachycardia, and ventricular fibrillation.</p> <p>Noncardiac: Congenital profound sensorineural hearing loss, syncope and sudden death. Long QTc interval usually >500 msec. More than 50% untreated individuals die prior to age 15.</p>	<ul style="list-style-type: none"> – Beta-blockers, pacemakers, and ICDs, – avoid drugs that prolong the QT interval and activities known to precipitate syncopal events.

700 msec. The risk of malignant ventricular arrhythmias is very high and usually occurs early in childhood. The average age of death in this disorder is 2.5 years (Splawski et al. 2006). Two forms of Timothy syndrome have been described, type 1 and type 2, but type 2 is extremely rare and has only been reported in two individuals (Splawski et al. 2006).

Genetic Basis of LQTS. In the mid-1990s, it was discovered that abnormalities of cardiac ion channel proteins were the underlying cause of LQTS. The mutations associated with LQTS are transmitted via the autosomal dominant route, with the exception of Jervell and Lange-Nielsen syndrome, which is autosomal recessive.

At least 8 genes have been associated with LQTS, indicating substantial genetic heterogeneity. There is also substantial allelic heterogeneity, as several hundred unique mutations have been identified within these genes. These genes code for proteins that regulate the transport of either sodium, potassium or calcium ions across cardiac cell membranes (Ackerman 2005) (Table 2).

For RWS, three phenotypes have been described and mutations in at least 5 different genes have been identified. Phenotypes 1 and 2 account for approximately 95% of RWS, and phenotype 3 is found in less than 5% of RWS. Phenotype 1 is associated with the genes *KCNQ1* and *KCNE1*; phenotype 2 is associated with *KNCH2* (*HERG*) and *KCNE2*; and phenotype 3 is associated with *SCN5A*. Approximately 60–70% of individuals with RWS will have a mutation in 1 of these 5 genes. Two other genes have been proposed as associated with RWS, *ANK2* and *KCNJ2*, but uncertainty exists as to whether they should be included as causes of RWS. *ANK2* does not encode a cardiac ion channel gene, as do the other genes. However, studies suggest that mutations in *ANK2* cause abnormal coordination of multiple functionally related ion channels and transporters (Mohler et al. 2005).

There is variable penetrance for the RWS, and penetrance may differ for the various subtypes. While linkage studies in the past indicated that penetrance was 90% or greater, more recent analysis by molecular genetics has challenged this number (Priori et al. 2001). It has been demonstrated that in at least some families, penetrance is low. Priori et al. (2001) studied family members of 9 patients who were thought to have de novo mutations in LQTS genes

based on the lack of other family members who were symptomatic. Of 46 family members tested, 15 (33%) were, in fact, found to be carriers of LQTS mutations. Penetrance for these families was calculated at 25% based on these data. The authors concluded that the mutations in these 9 patients were not de novo mutations, but rather represented inherited mutations with low penetrance.

Genetic testing for LQTS. A commercial test for LQTS genetics has been available since 2004 through PGx Health, New Haven, CT. The test, called the Familion® genetic test, analyzes the 5 genes associated with RWS. The patient's DNA is first extracted from whole blood. Genetic sequencing of the coding regions and intron/exon splice sites of all 5 genes is then performed in both forward and reverse sequence. The sequences are read independently by two technologists, with discrepancies resolved by an experienced supervisor. Variants that are detected in this initial analysis are confirmed by repeating the sequencing twice in the forward and twice in the backward direction. Final results are reviewed by a doctoral-level scientist and by the lab director prior to reporting of results to clinicians.

The mutation analysis described above is termed “comprehensive” testing, i.e., any deleterious mutations are sought using DNA amplification via polymerase chain reaction (PCR) to generate templates for sequencing. Mutation analysis can also be performed in a specific fashion, i.e., testing for the presence of a known mutation that has previously been identified in the family. For specific testing, sequences from the test are compared with reference standards containing the mutation previously identified in a family member.

Comprehensive testing can detect mutations in about 70% of individuals with a clinical diagnosis of RWS. This suggests other yet-to-be-identified genes are present or the technology used is missing mutations in known genes. Results from comprehensive mutation analysis will reveal the location of any variant (i.e., whether it is in a critical functional domain), the type of mutation involved (e.g., missense, nonsense, deletion/insertion) and the effect of that mutation on the transcript (mRNA) or protein product. These factors are all taken into account in determining the likelihood that a mutation identified is pathological, or whether it represents a benign polymorphism.

Table 2. Genetic Features of Congenital Long QT Syndromes

Form of Congenital LQT	Genes	Inheritance	De novo Mutation Rate	Mutation Detection Rate	Penetrance
Romano-Ward Syndrome (RWS) ^a	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> , (possibly <i>ANK2</i> and <i>KCNJ2</i>)	autosomal dominant	“small”, most affected individuals have an affected parent	70% for all 5 genes ^b	LQT1 phenotype, 93% LQT2 phenotype, 46% LQT3 phenotype, 18%
Andersen-Tawil Syndrome	<i>KCNJ2</i>	autosomal dominant	50%	60% ^c	80-94% ^d
Timothy Syndrome, types 1 and 2	<i>CACNA1C</i>	autosomal dominant	100% ^e	Type 1, 100%. G406R mutation is only known mutation Type 2, unknown	100%
Jervell and Lange-Nielsen Syndrome	<i>KCNQ1</i> (<i>LQT1</i>) or <i>KCNE1</i> (<i>LQT5</i>)	autosomal recessive	N/A	Unknown	Unknown

^a There are 3 phenotypes described for RWS; 55–60% of RWS patients have the LQT1 phenotype due to *KCNQ1* and *KCNE1* mutations; 35-40% have the LQT2 phenotype due to *KCNH2* and *KCNE2* gene mutations, and 3–5% have the LQT3 phenotype due to *SCN5A* gene mutations.

^b Mutation scanning and/or sequence analysis of coding regions.

^c Sequencing of the entire coding region (2 exons, 5.4 kb); the R218W mutation is common

^d 60% of affected individuals have the triad of cardinal features, 80% express only 2 of the 3 features, and non-penetrance is seen in 6–20% of individuals with an identifiable mutation.

^e Germline mosaicism has been reported; offer prenatal diagnosis to couples with affected child

Variants are placed into 4 classes, based on the above factors (Familion® Web site and PGxHealth personal communication, 8/9/07):

- Class I – Deleterious and probable deleterious mutations. These are either mutations that have previously been identified (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations).
- Class II – Possible deleterious mutations. These variants encode changes to protein(s), but occur in regions that are not considered critical. Approximately 5% of patients without LQTS will exhibit mutations in this category.
- Class III – Variants not generally expected to be deleterious. These variants encode modified protein(s), however, these are considered more likely to represent benign polymorphisms. Approximately 90% of patients without LQTS will have one or more of these variants, therefore, patients with only class III variants are considered negative.
- Class IV – Non-protein-altering variants. These are not considered to have clinical significance and are not reported in the results of the Familion® test.

Clinical Manifestations. There is a wide range of clinical expression in LQTS. RWS is often asymptomatic and is not associated with noncardiac clinical features; therefore, the diagnosis may be suspected in one of several situations. In approximately one-third of patients, symptoms of syncope, ventricular arrhythmias, and/or cardiac arrest, are present, and cannot be explained by other potential etiologies. Other times, a prolonged QT interval is noticed on electrocardiography done for other purposes. Third, a family member may experience cardiac arrest or sudden death, leading to a diagnosis of LQTS, and thus raising the possibility of LQTS in other family members.

The major sign of RWS is a prolonged or borderline prolongation of the QT interval on electrocardiography. However, the length of the QT interval is variable in this disorder, and is not prolonged in all patients with RWS. This results in a fairly large degree of overlap in the length of the QT interval for patients with and without LQTS. This is shown in the Figure, in which the distribution for the QT interval in patients with

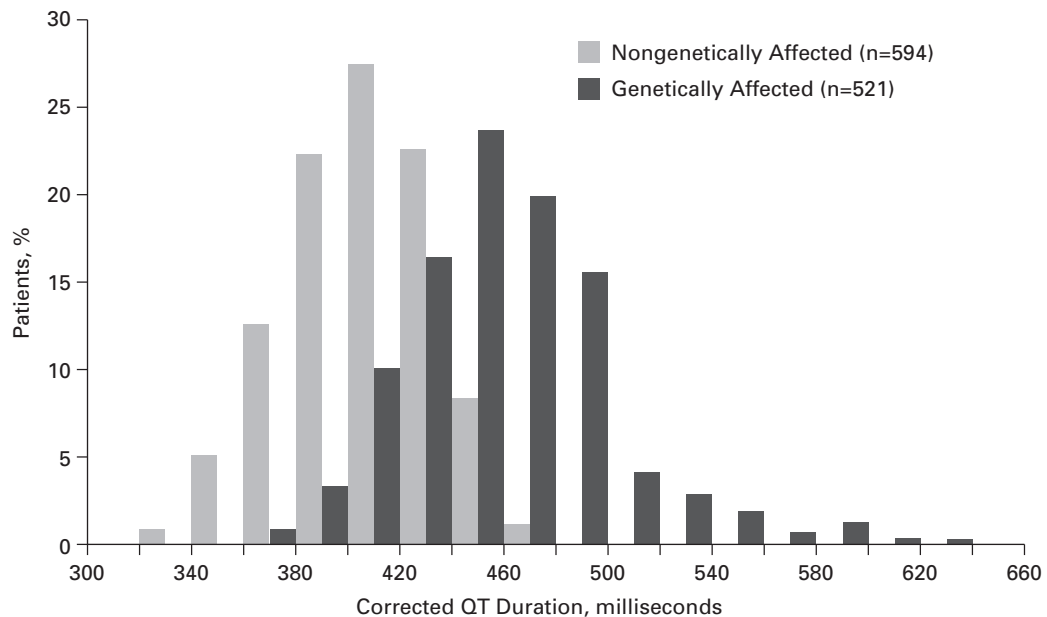
a genetic mutation for LQTS is superimposed over the distribution for patients without a genetic mutation. As seen in this graph, there is substantial overlap in the QT interval between these two populations, especially in the range of 400–450 msec.

The length of the QT interval is correlated with the severity of the disorder and the risk of malignant ventricular arrhythmias. The typical cut-off for a “normal” QT interval is 440 msec. However, this cutoff will incorrectly classify at least 5–10% of patients with LQTS who have a shorter QT interval. Some experts have suggested that a QT interval of less than 410 msec can be used to rule out LQTS, and that a QT interval of greater than 470 msec in men and greater than 480 msec in women can be considered definitely abnormal (Chiang and Roden 2000). This is based on an analysis of 199 patients with LQTS in which no affected gene carriers had a QT interval less than 410 msec and no normal patients had a QT interval of greater than 470 msec (greater than 480 msec in women).

Other morphologic abnormalities of T-waves may be seen on EKG (Chiang and Roden 2000). These include broad-based or notched T-waves, and a prolonged T-wave duration. T-wave alternans, defined as beat-to-beat alternation of T-wave morphology, can also be seen. This finding is sometimes seen at rest, but more commonly is precipitated by physical or emotional stress. T-wave alternans may be a precursor to malignant ventricular arrhythmias and therefore has been proposed as a marker for patients who are at high risk for arrhythmias (see related 2007 TEC Assessment, “Microvolt T-Wave Alternans Testing to Risk-Stratify Patients Being Considered for ICD Therapy for Primary Prevention of Sudden Death,” Vol. 21, No. 14).

Diagnosis of LQTS. For LQTS syndromes other than RWS, the diagnosis can be made through the presence of other congenital defects, for example bilateral deafness in the Jervell and Lange-Nielsen. For RWS, the diagnosis has traditionally been based on a combination of family history, clinical symptoms, and findings on electrocardiography (Chiang and Roden 2000).

The length of the QT interval is not by itself a reliable method for diagnosing LQTS. As shown in the Figure, a QT interval in the

Figure. Comparison of QT Distribution in Affected vs. Unaffected Members of Families with LQTS

(Reproduced with permission from Napolitano et al. 2005)

range of 400–450 msec cannot be used to discriminate patients with and without the long QT syndrome. This leads to difficulty in diagnosing the disorder in many patients and under-recognition of the syndrome in clinical care (Maron et al. 2007). Conversely, there is a potential for overdiagnosis in patients with a borderline or slightly prolonged QT interval if clinicians do not appreciate the overlap in these populations (Taggart et al. 2007). A borderline or slightly prolonged QT interval in a patient without other signs and symptoms of LQTS is much more likely to represent a normal variant rather than the LQTS.

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS (Schwartz et al. 1995). The most recent version of this scoring system is shown in Table 3. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2–3 an intermediate probability; and 1 or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system, therefore, the accuracy of this scoring system is ill-defined. However, it is now possible to use genetic testing as the gold standard, thus allowing calculation of performance characteristics compared to genetic testing (Hofman 2007). Evidence on the performance characteristics

of the clinical criteria for diagnosis will be discussed in the Review of Evidence.

Simplified diagnostic criteria have also been offered by Keating et al. (1992) based solely on an elongated QT interval in the absence of syndactyly or congenital deafness. Using these criteria, the likelihood of asymptomatic patients having LQTS is shown in Table 4. For patients with typical symptoms of LQTS such as syncope or documented ventricular arrhythmias, the cutoff for the QT interval is lowered to 450 msec.

Treatment of LQTS

A sudden increase in sympathetic activity is probably the most common trigger for ventricular arrhythmias. Therefore, antiadrenergic treatment is a focus of treatment strategies (Priori et al. 2001). Antiadrenergic treatment with beta blockers is considered the treatment of choice for most patients with RWS. Avoidance of situations that might cause an increase in sympathetic activity, such as strenuous activity, is also recommended for most patients. Cardiac sympathectomy, i.e., denervation of the sympathetic nerves to the heart, is a treatment option for patients who continue to have symptomatic episodes despite beta-blocker treatment, or in patients who are unable to take beta blockers.

Table 3. Diagnostic Scoring System for LQTS (Adapted from Schwartz et al. 1993)

Criteria	Points
Electrocardiographic findings	
QT _c >480 msec	3
QT _c 460–470 msec	2
QT _c <450 msec	1
History of torsades de pointes	2
T-wave alternans	1
Notched T-waves in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope brought on by stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS	1
Unexplained sudden death at age <30 years in immediate family members	0.5

Table 4. Keating Criteria for Diagnosis of LQTS (adapted from Vincent 2005)

	% of Affected Individuals	QT (corrected)	
		Males	Females
Positive LQTS	68%	>470 msec	>480 msec
Uncertain LQTS	20%	450–460 msec	460–470 msec
	11%	400–450 msec	400–450 msec
Negative LQTS	<1%	<400 msec	<400 msec

The use of automatic implantable cardiac defibrillators (ICDs) has become more common in the last decade; however, indications for their use in RWS have not been firmly established. ICDs are definitely indicated in patients with prior aborted cardiac arrest and in patients who have symptoms despite treatment with beta blockers. For other patients, the decision to utilize an ICD is dependent on the risk for sudden death. In an analysis of registry patients, Zareba and colleagues (2003) examined the indications for 125 patients who had been treated with an ICD at the discretion of their treating physicians. Of these 125 patients, 43% (54/125) had experienced a prior aborted cardiac arrest, 15% (19/125) had recurrent syncope despite treatment with beta-blocker therapy, and 42% (52/125) had other indications. The most common other indications were syncope and a family history of sudden

death. These authors also identified many patients in the registry who had indications of prior cardiac arrest and/or recurrent syncope despite beta-blocker treatment, but who were not treated with an ICD, thus indicating a large degree of variability in ICD use among treating physicians.

Some experts advocate wider use of ICDs given that some patients treated with beta blockers will experience sudden death. Others caution that more widespread use of ICDs may lead to an overall decrease in quality of life for treated patients due to inappropriate shocks in many patients who never experience sudden cardiac arrest. The level of risk that should warrant ICD insertion has yet to be standardized for patients with RWS. Nevertheless, attempts at risk stratification are often part of the clinical decision-making when an ICD is considered.

Risk stratification can be performed using multiple factors, including symptoms, the length of the QT-interval, family history, and determination of LQTS subtype.

Methods

Search Methods

MEDLINE® was searched (via PubMed) using the terms “long QT syndrome” OR “LQTS,” cross-referenced with the terms “genetics” OR “gene” from 1990 through October 2007, limited to English-language articles on human subjects. Electronic searches were supplemented with the “related articles” function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies. Searches for Web-based information were initiated through the Web site www.genetests.org, and through the Web site of the manufacturer of the LQTS genetic test, www.pgxhealth.com.

Study Selection

Studies were selected for inclusion in this Assessment that included primary data on patients with LQTS, and relevant evidence for one or more of the key questions in the following categories:

- Diagnostic accuracy of clinical methods for diagnosing LQTS
- Diagnostic accuracy of genetic testing for LQTS
- Prognosis of LQTS by specific syndrome and/or LQTS subtype
- Outcomes of treatment with beta-blocker medications or ICD therapy, including information on at least one cardiovascular event (e.g., syncope, documented ventricular arrhythmia, aborted sudden cardiac death, cardiac arrest, sudden cardiac death)

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on October 17, 2007. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate.

Formulation of the Assessment

Patient Indications

General indications for genetic testing for LQTS include patients with known or suspected LQTS. Within this broad category, there are numerous subpopulations that may have differing likelihood of LQTS, different clinical expression, and differential response to treatment.

“Diagnostic testing” will refer to situations where the genetic test is used to confirm a diagnosis of LQTS in patients who do not meet the clinical criteria for LQTS. “Prognostic testing” will refer to situations in which the patient already has a diagnosis of LQTS confirmed by clinical criteria, and testing is intended to determine prognosis and/or direct therapy.

Technologies to Be Compared

The use of genetic testing will be compared to no genetic testing, i.e., diagnosis or prognosis of LQTS by clinical criteria alone.

Health Outcomes

The main health outcomes to be considered will be the morbidity and mortality associated with LQTS-related arrhythmias. The most common manifestations of these arrhythmias are palpitations, syncope, and cardiac arrest. Cardiac arrest may be aborted, either spontaneously or as a result of cardiopulmonary resuscitation. If cardiac arrest is not aborted, then sudden death results.

For the purpose of this Assessment, health outcomes will be grouped into three categories: 1) “any cardiovascular event” refers to documented ventricular arrhythmia, syncope, cardiac arrest, and/or sudden death; 2) “cardiac arrest” will refer to both resuscitated and non-resuscitated arrests; 3) “sudden death” will refer to patients who die as a result of ventricular arrhythmias and cardiac arrest.

Specific Assessment Questions

Does the use of genetic testing improve health outcomes for patients with known or suspected LQTS?

There is no direct evidence to answer the question of primary interest. Therefore, we sought indirect evidence to establish a causal chain: that genetic testing improves the diagnosis of LQTS, resulting in changes in management

that improve health outcomes. The chain for prognostic use is that genetic testing provides additional information that resulting in changes in management that improve health outcomes. As with TEC Assessments of other genetic tests, we apply the assessment framework recommended by EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Workgroup, an initiative of the National Office of Public Health Genomics at the Centers of Disease Control and Prevention. The EGAPP framework addresses analytic validity, clinical validity and the clinical utility of a genetic test.

1. Analytic validity of genetic testing
 - What is the analytic validity of genetic testing for this disorder?
 - Does genetic testing detect a mutation that is present (analytic sensitivity)?
 - Does genetic testing report a negative result when a mutation is not present (analytic specificity)?
2. Clinical validity of genetic testing
 - What is the diagnostic accuracy of genetic testing for this disorder?
 - If genetic testing identifies new cases of disease, or otherwise reclassifies patients by disease status or severity, are these newly reclassified cases similar to those identified by clinical methods?
3. Clinical utility of genetic testing
 - Is treatment for this condition effective?
 - Does genetic testing provide information on risk stratification that will influence clinical decisions?
 - Does genetic testing provide information on expected response to treatment that will influence clinical decisions?

Review of Evidence

The use of genetic testing for LQTS can be grouped into two major categories. The first is to establish a diagnosis of LQTS, which will be termed “diagnostic testing.” The second is to identify the specific subtype of LQTS and/or the specific genetic mutation present in patients who are known to have LQTS in order to determine prognosis and/or direct therapy. This category will be termed “prognostic testing.” The evidence will be reviewed separately in each of these categories. Within each category, specific populations will be discussed that are most likely to derive benefit from genetic testing.

Genetic Testing to Establish the Diagnosis of LQTS (Diagnostic Testing)

In this setting, the diagnosis of LQTS is not certain, and genetic testing is intended to confirm or exclude the diagnosis. Patients may be symptomatic or asymptomatic, but have a Schwartz score less than 4 and/or fail to meet other diagnostic criteria for LQTS.

When used to establish the diagnosis of LQTS, several conditions must be satisfied in order to determine that the test improves health outcomes. First, the test must have sufficient diagnostic accuracy for the intended use and must improve on the ability to make the diagnosis above existing methods. Second, the diagnostic information must lead to important changes in the clinical management of patients. Lastly, these changes in management must lead to improvements in health outcomes. The following questions address each component of this chain of logic:

1. What is the analytic validity of genetic testing for this disorder?
 - Does genetic testing detect a mutation that is present (analytic sensitivity)?
 - Does genetic testing report a negative result when a mutation is not present (analytic specificity)?

No published studies were identified in the peer-reviewed literature that contained data on the analytic validity of genetic testing for LQTS. The following information on analytic sensitivity and specificity was obtained from the web site of PGxHealth (New Haven, Conn.), the manufacturer of the Familion[®] genetic test for LQTS. Additional unpublished data was supplied by PGxHealth in response to questions submitted by the TEC staff (PGxHealth, personal communication).

Analytic Sensitivity. The PGxHealth Web site states the following: “Failure to detect a variant in an analyzed amplicon could be due to that amplicon being refractory to analysis by direct DNA sequencing, sample mishandling, sample tracking errors or errors in data analysis. The rate of such errors is estimated to be <1%.” (PGxHealth Web Site).

This analytic sensitivity is based on an independent analysis of 21 “unknown” samples by PGxHealth, which had been previously characterized and supplied to the company by a research lab at the University of Rochester.

Of these 21 samples, 20 contained various types of mutations including nonsense, missense, splice site, and insertions/deletions, and one sample was a “wild type,” containing no mutations. According to the manufacturer, all of the mutations were correctly identified (PGxHealth, personal communication, 7/20/07), thus, leading to their reporting of analytic sensitivity greater than 99%.

Analytic Specificity. The PGxHealth Web site states the following: “The chance of a falsely detected genetic variant is minimized by requiring that each variant be seen in sequence traces for both forward and reverse directions and that two trained technicians independently examine each trace. Chances of false positives are minimized by the use of a validated sample tracking system that uses robotics and barcodes. For each positive finding of a Class I or Class II variant, a second round of PCR amplification and sequencing is performed to confirm the initial finding.”

During the same validation process described for the analytic sensitivity, 5 “unknown” normal samples without mutations, each containing 13,414 base sequences, were also sequenced. No false-positive results (deleterious mutations) were reported from this analysis (PGxHealth, personal communication, 7/20/07).

Abnormal results from the commercial test are reported as Class I or Class II mutations. Approximately 75% of all reported deleterious mutations are Class I and the remaining 25% are Class II mutations (Tester 2007). For Class I mutations, data from the validation sample reported by the manufacturer indicate that false-positive results are expected to be extremely uncommon, so that analytic specificity will approach 100%. For Class II mutations, false-positive results are more likely to occur. Analysis of non-LQTS patients revealed that variants reported as Class II mutations are found in approximately 5% of patients without LQTS (PGxHealth, personal communication, 8/9/07). Therefore, the analytic specificity of Class II mutations is expected to be approximately 95%.

2. What is the clinical sensitivity and specificity of genetic testing for the diagnosis of LQTS?

The true clinical sensitivity and specificity of genetic testing for LQTS cannot be determined

with certainty as there is no independent gold standard for the diagnosis of LQTS. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate gold standard.

Hofman et al. (2007) performed the largest study comparing clinical methods with genetic diagnosis, using registry data. This study compared multiple methods for making the clinical diagnosis, including the Schwartz score, the Keating criteria, and the absolute length of the QTc with genetic testing (Table 5). This data indicates that only a minority of patients with a genetic mutation will meet the clinical criteria for LQTS. Using the most common clinical definition of LQTS, a Schwartz score of 4 or greater, only 19% of patients with a genetic mutation met the clinical criteria. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic mutation who met clinical criteria was still relatively low, improving to only 48% when a cutoff of 2 or greater was used. When the Keating criteria were used for clinical diagnosis, similar results were obtained. Only 36% of patients with a genetic mutation met the Keating criteria for LQTS.

The best overall accuracy was obtained by using the length of the QTc as the sole criterion, however, even this criterion achieved only modest sensitivity at the expense of lower specificity. Using a cutoff of 430 msec or greater for the QT interval a sensitivity of 72% and a specificity of 86% was obtained.

Two studies evaluated the percent of individuals with a clinical diagnosis of LQTS that are found to have a genetic mutation (Table 5). These two studies indicate that genetic testing will identify most individuals with a clinical diagnosis, but will fail to identify a deleterious mutation in up to 30% of individuals with a clinical diagnosis.

Tester et al. (2006) provided the largest study sample, consisting of 274 consecutive patients referred for genetic testing and found to have a LQTS mutation. The genetic diagnosis was compared to the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of all patients with a clinical diagnosis of LQTS, 72% were found to have a genetic mutation. Choi et al. (2004) reported results for a smaller, more highly selected subgroup of near-drowning victims. In this study, for patients with a clinical

Table 5. Diagnostic Accuracy of Clinical Methods and Genetic Testing for LQTS

Study/Yr	Pt Population	Clinical Diagnosis	Clinical Validity of Genetic Testing	
			Sensitivity	Specificity
Sensitivity and Specificity of Clinical Diagnosis (using genetic testing as gold standard)				
Hofman et al. 2007	<ul style="list-style-type: none"> - 513 relatives of 77 probands diagnosed with LQTS - 208/513 found to have genetic mutation 	LQTS diagnosed by one of several methods: <ul style="list-style-type: none"> - Schwartz score ≥ 4 - Schwartz score ≥ 3 - Schwartz score ≥ 2 - Keating criteria** - QT_c ≥ 430 msec 	19% (41/208) 36% (79/208) 48% (126/208) 36% (88/208) 72% (194/208)	99% 99% 91% 99% 86%
Shimizu et al. 2004	<ul style="list-style-type: none"> - 95 patients with LQTS and genotype LQT1, from 37 unrelated Japanese families 	LQTS diagnosed by one of two methods: <ul style="list-style-type: none"> - Schwartz score ≥ 4 - Keating criteria** 	51% (48/95) 64% (61/95)	NA NA
Sensitivity and Specificity of Genetic Diagnosis (using clinical diagnosis as gold standard)				
Tester et al. 2006	<ul style="list-style-type: none"> - 541 consecutive unrelated pts referred to Mayo Clinic for genetic testing. - 272/541 patients with genetic mutation for LQTS 	<ul style="list-style-type: none"> - LQTS diagnosis by Schwartz score ≥ 4, blinded to genetic testing. - 123 pts with definite LQTS by Schwartz score. 	72% (72/123)	57%* (122/215)
Choi et al. 2004	<ul style="list-style-type: none"> - 43 pts with fatal or near-fatal drowning, drawn from 388 consecutive pts referred to Mayo Clinic for genetic testing 	<ul style="list-style-type: none"> - LQTS diagnosis by Schwartz score ≥ 4, blinded to genetic testing. - 33/43 pts with definite LQTS by Schwartz score. 	91% (30/33)	100% (10/10)

* Calculated specificity using Schwartz score of 4 or greater as gold standard; however, many patients with LQTS will have Schwartz score <4.

** Keating criteria positive if QTc greater than 470 msec regardless of symptoms, or greater than 450 msec in the presence of typical symptoms

diagnosis of LQTS, 91% were found to have a genetic mutation.

3. If genetic testing identifies new cases of disease, or otherwise reclassifies patients by disease status or severity, are these newly reclassified cases similar to those identified by clinical methods? Do they derive a similar benefit from treatment?

Two studies provide relevant evidence on this question (Table 6). These studies compare that there is a large degree of overlap in the two populations.

Two studies provide relevant evidence on this question (Table 7). These studies compare outcomes in clinically identified probands with those of family members identified by genetic testing. Both studies are based on data from the International LQTS registry, therefore it is likely Results of the two studies indicate that patients identified by genetic testing have a lower likelihood of cardiovascular events compared with probands. However, a significant minority of patients identified by genetic testing experienced cardiovascular events (22%), and some experienced cardiac arrest/sudden death (4%).

Locati et al. (1998) also reported the median number of cardiovascular events per year in both groups. Probands had an event rate (0.24/year) that was more than twice as high as that of genetically affected family members (0.11/year). The event rate in affected family members indicates that each year approximately one in 10 individuals will experience a cardiovascular event.

4. Is treatment for this condition effective?

The evidence on treatment efficacy of beta blockers consists of case series and pre-post studies, as summarized in Table 7. The two pre-post studies summarized in Table 7 provide the strongest evidence. Both studies reported large decreases in any cardiovascular events and smaller decreases in cardiac arrest and/or sudden death. Priori et al. (2004) compared unequal time periods pre- and post-initiation of treatment, 21 years pretreatment compared with 5.2 years post-treatment thus reducing the validity of their comparison. Moss et al. (2000) compared a 5-year time period pre- and post-initiation of treatment. These authors reported that symptoms were reported in less than half as many patients following initiation of beta

blockers; this reduction was significant at the $p < 0.001$ level. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant at $p < 0.001$.

Sauer et al. (2007) performed a multivariate Cox proportional hazards analysis on the efficacy of beta-blocker therapy in 812 adults with genotype positive LQTS. These authors reported a risk reduction of approximately 60% in patients treated with beta-blockers for both the first cardiac event after 18 years of age (HR 0.41; 95% CI: 0.27–0.64) and for death or aborted sudden death after 18 years of age (HR 0.40; 95% CI: 0.17–0.98).

The case series provide little further evidence on the treatment efficacy of beta-blockers, but can be useful in determining the frequency of cardiac events occurring while on treatment. As shown in Table 7, the data indicate that a substantial minority of patients experience LQTS-related symptoms while on treatment with beta-blockers, including a small number of patients who experience sudden death. While this data is not sufficiently rigorous to determine the precise rate of events while on treatment, it does indicate that beta blockers are not 100% effective in preventing ventricular arrhythmias.

It is unlikely that randomized trials can be performed to better evaluate the treatment efficacy of beta blockers, since it would be considered unethical to withhold treatment with beta blockers given the possibility of increased mortality.

One published study was identified that reported on outcomes of treatment with ICDs (Zareba et al. 2003) (Table 7). This study identified patients in the LQTS registry who had been treated with an ICD at the discretion of their treating physician. Patients were categorized into three main indications for ICD: 1) a prior history of aborted cardiac arrest, 2) recurrent symptoms despite treatment with beta blockers, and 3) other. Patients in the registry who were not treated with an ICD, but had the same indications, were used as a control group. The authors reported that outcomes were better for patients with an ICD compared to those without, and in some cases the differences between groups reached statistical significance. However, the validity of these comparisons is limited by several factors. The patient groups

Table 6. Differential Prognosis for Genetically Identified vs. Clinically Identified Individuals

Study/Yr	Study Design	Pt Population	Group	Outcomes		
				QTc Interval	Any Clinical Event*	Aborted SCD or SCD
Moss et al. 2000	Analysis of prospectively collected registry data	869 pts in LQTS registry treated with beta blockers	Probands		80% (462/581)	17% (100/581)
			Affected family members		32% (92/288)	4% (11/288)
Locati et al. 1998	Analysis of prospectively collected registry data	479 probands identified clinically and 1041 affected family members from the LQTS registry			Median events/yr	
			Probands	517 ± 591	76% (365/479)	0.24 ¹
			Affected family members	483 ± 391	22% (233/1041)	0.11 ¹

¹ QTc value for females, value for males similar

Table 7. LQTS Treatment Efficacy

Study/Yr	Study Design	Pt Population	Treatment Group	Outcomes			
				Any Clinical Event ¹	Aborted SCD or SCD	SCD	Adverse Events
Treatment with Beta Blockers							
Schwartz et al. 2006	Retrospective case series, including cases from literature reports (31% of total).	186 pts with Jervell and Lange-Nielsen Syndrome.	Beta blockers (n=92 with sufficient information); median duration of treatment 8 yrs	51% (47/92)	27% (25/92)	16% (15/92)	NR
Schwartz et al. 2001	Retrospective case series, including registry data (50% of total)	670 pts with LQTS and known genotype LQT1 (n=371), LQT2 (n=234), or LQT3 (n=65)	Beta blockers: LQT1 (n=162) LQT2 (n=91) LQT3 (n=18)	19% (31/162)* 41% (37/91) 50% (9/18)	4.3% (7/162) 4.4% (4/91) 17% (3/18)		
				* p<0.001 vs. LQT2; p=0.05 vs. LQT3			
Dorostkar et al. 1999	Retrospective case series Mean duration of follow-up 6.3 years	37 patients with idiopathic LQTS; 36/37 symptomatic	Combined beta-blockade and continuous pacemaker therapy	All pts: 27% (10/37) Compliant pts: 17% (5/30)		8.1% (3/37)	5 pts with pacemaker malfunction; 3 symptomatic

Table 7. LQTS Treatment Efficacy (cont'd)

Study/Yr	Study Design	Pt Population	Treatment Group	Any Clinical Event ¹		Aborted SCD or SCD	
				Pre-	Post-	Pre-	Post-
Treatment with Beta Blockers (cont'd)							
Priori et al. 2004	Prospective (?) case-series/cohort; registry data mean duration pretreatment 21 years; mean duration post-treatment 5.2 years; pre-post comparison of outcomes	335 pts with known LQTS genotype LQT1, LQT2, or LQT3 and treated with beta blockers	Beta blockers;				
			All pts (n=355)	47% (159/335)	16% (55/335)	5.7% (19/335)	4.2% (14/335)
			LQT1 (n=187)	39% (73/187)	10% (19/187)	2.1% (4/187)	1.1% (2/187)
			LQT2 (n=120)	58% (70/120)	23% (27/120)	8.3% (10/120)	6.6% (8/120)
		LQT3 (n=28)	57% (16/28)	32% (9/28)	18% (5/28)	14% (4/28)	
Moss et al. 2000	Prospective case series/cohort; registry data; pre-post comparison of outcome using matched time periods of 5 years	869 pts with LQTS diagnosed by clinical or genetic methods, and treated with beta blockers. Subset of 139 pts with genotype determined as LQT1, 2 or 3	Beta blockers:				
			Probands	80% (462/581)	33% (194/581)*	17% (100/581)	9% (50/581)*
			Family members	32% (92/288)	17% (49/288)*	4% (11/288)	4% (11/288)
			LQT1 (n=69)	57% (39/69)	19% (19/69)*	10% (7/69)	3% (2/69)
			LQT2 (n=42)	57% (24/42)	36% (15/42)*	10% (4/42)	5% (2/42)
		LQT3 (n=28)	14% (4/28)	14% (4/28)	0% (0/28)	10% (3/28)	
				*p<0.001		*p<0.001	

Table 7. LQTS Treatment Efficacy (cont'd)

Study/Yr	Study Design	Pt Population	Treatment Group	Outcomes			
				Any Clinical Event ¹	Aborted SCD or SCD	SCD	Adverse Events
Treatment with Automatic Implantable Cardiac Defibrillators (ICD)							
Zareba et al. 2003	Retrospective analysis of registry data	125 pts who had ICD implanted in three groups ² . 89 pts with aborted cardiac arrest but no ICD. 72 pts with syncope on beta-blockers but no ICD.	Cardiac arrest				
			ICD (n=54)	17% (9/54)*	4% (2/54)*	0% (0/54)**	
			No ICD (n=89)	55% (49/89)	10% (11/89)	19% (17/89)	
			Syncope on beta blockers				
			ICD (n=19)	26% (5/19)**	0% (0/19)*	5% (1/19)*	
			No ICD (n=72)	67% (48/72)	3% (2/72)	13% (9/72)	
				*p=NS	*p=NS	*p=NS	
				**p=0.002		**p<0.001	

1 Syncope, documented malignant arrhythmia, aborted sudden cardiac death, or sudden cardiac death

2 Categorized into following indications: 1) prior cardiac arrest, 2) recurrent syncope despite beta-blocker treatment, and 3) other.

differed on a number of clinical characteristics, including whether they were probands versus affected family members and whether they had a history of prior documented ventricular arrhythmias. The groups also differed in respect to other treatments, with a greater percentage of ICD patients treated with beta-blockers compared to non-ICD patients (91% vs. 74%, $p=0.02$). The length of follow-up time was also different between groups, with the non-ICD patients followed longer than the ICD patients (9 ± 7 vs. 3 ± 3 years, $p<0.001$), and the results were not corrected for the difference in follow-up.

Genetic Testing to Determine LQTS Subtype, and/or Specific Genetic Mutation (Prognostic Testing)

In this situation, the diagnosis of LQTS has been established by clinical methods. Genetic testing can identify the specific LQTS syndrome, the specific subtype of a given syndrome, or the specific mutation present for the index patient in order to determine prognosis and/or direct treatment decisions.

In order to demonstrate that genetic testing improves health outcomes in this situation, several conditions must be met. First, the genetic test must be able to identify clinically relevant subgroups of patients. Second, these subgroups must demonstrate variable prognosis and/or response to treatment. Thirdly, these differences in prognosis and/or treatment response must lead to changes in management decisions. Finally, these changes in management decisions must lead to improved health outcomes. The following questions address each step in this chain of logic:

5. Does genetic testing for LQTS provide information on risk stratification that will influence clinical decisions?

The evidence suggests that different subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. This evidence is from case series and prospectively collected registry data, and is summarized in Table 8.

Among the syndromes, there appears to be relatively large differences in risk of clinical events. For example, Schwartz et al. (2006) compared 186 patients with Jervell and Lange Nielsen syndrome with 670 patients with Romano-Ward syndrome (Table 10), and

reported that cardiac arrest/sudden death was more than twice as common in patients with Jervell and Lange Nielsen syndrome.

Several reports have compared rates of cardiovascular events in subtypes of Romano-Ward syndrome (Priori et al. 2004; Priori et al. 2003; Schwartz et al. 2001; Zareba et al. 1998). These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the four studies (Priori et al. 2003, 2004; Schwartz et al. 2001) report that patients with LQT2 have higher event rates than patients with LQT1, while Zareba et al. (1998) report that patients with LQT1 have higher event rates than patients with LQT2.

Priori et al. (2003) analyzed risk factors for the likelihood of first cardiac event before the age of 40 in a Cox proportional hazards analysis. Using a combination of gender, the QTc interval and genetic testing, risk groups were derived (Table 9).

This data provides indirect evidence on whether treatment decisions could be affected by knowledge of LQTS subtype. In other words, if a subgroup can be defined with a very low risk of a cardiovascular event prior to age 40, then that group may not require treatment. The lowest risk group identified in this study (less than 30%) is not likely to be sufficiently low risk to justify withholding of treatment with beta blockers.

Sauer et al. (2007) also performed a multivariate Cox proportional hazards analysis of risk of cardiac events by LQTS subtype, controlled for gender, prior cardiac events, length of QTc interval, and beta-blocker therapy. This analysis revealed a significantly increased risk for LQT2 genotype (HR 2.27; 95% CI: 1.67–3.10) compared to LQT1, with no significant difference in risk for LQT3 compared to LQT1 (HR 1.15; 95% CI: 0.63–2.12).

In summary, these data suggest that there are differences in prognosis based on LQTS genotype and that information on genotype can contribute to risk stratification. However, there is not sufficient evidence to conclude that the information obtained from genetic testing on risk assessment leads to important changes in clinical management. Most patients will be treated with beta blockers and lifestyle medications, and it has not been possible to identify a

Table 8. Differential Prognosis by LQTS Genetic Subpopulations

Study/Yr	Study Design	Pt Population	Risk Group(s)	Outcomes			
				Any Clinical Event ¹	Aborted SCD or SCD	SCD	Other/Comment
Sauer et al. 2007	Analysis of prospectively collected registry data	812 adults (≥18yo) with genotype positive LQT1, LQT2, or LQT3	LQTS subtype: LQT1 (n=428) LQT2 (n=302) LQT3 (n=82)	20% (83/428) 33% (97/302) 15% (12/82)	4.9% (21/428) 8.0% (25/302) 4.9% (4/82)	1.2% (5/428) 3.7% (12/302) 3.7% (3/82)	Event rates refer to events occurring in adulthood only.
Schwartz et al. 2006	Analysis of prospectively collected data	186 patients with Jervell and Lange-Nielsen syndrome. 670 pts with other types LQTS from database	JLN syndrome Romano-Ward Syndrome		39% (72/186) 18% (89/492)		p value NR
Priori et al. 2004	Analysis of prospectively collected registry data; mean f/u 21 years	335 pts with known LQTS genotype LQT1, LQT2, or LQT3 and treated with beta-blockers	LQTS subtype: LQT1 (n=187) LQT2 (n=120) LQT3 (n=28)	39% (73/187) 58% (70/120) 57% (16/28)			
Shimizu et al. 2004	Retrospective (?) case series	95 pts from 37 families in Japan with mutation in KCNQ1 region (LQT1). Length of f/u not specified	Location of mutation: Transmembrane (n=66) C-terminus (n=29)	55% (36/66) 21% (6/29)*	15% (10/66) 0% (0/29)*		Schwartz score: 4.4 ± 2.1 2.0 ± 1.5 p<0.0001
Priori et al. 2003	Analysis of prospectively collected data	647 patients from 193 consecutive families with LQTS	LQTS subtype: LQT1 LQT2 LQT3	30% (116/386) 46% (95/206) 42% (23/55)	9.6% (37/386) 20% (41/206) 16% (9/55)		p=0.022

Table 8. Differential Prognosis by LQTS Genetic Subpopulations (cont'd)

Study/Yr	Study Design	Pt Population	Risk Group(s)	Outcomes			
				Any Clinical Event ¹	Aborted SCD or SCD	SCD	Other/Comment
Schwartz et al. 2001	Analysis of prospectively collected data	670 pts with LQT1-3 and symptomatic	LQTS subtype:				
			LQT1		28% (104/371)		
			LQT2		40% (94/234)		
			LQT3		49% (32/65)		
					p value NR		
Zareba et al. 1998	Analysis of prospectively collected data	246 pts with LQTS and LQT1-3 genotype	LQTS subtype:				
			LQT1	62% (70/112)	9% (10/112)		
			LQT2	46% (33/72)	5.6% (4/72)		
			LQT3	18% (11/62)	6.5% (4/62)		
				p<0.0012			

¹ Syncope, documented malignant arrhythmia, aborted sudden cardiac death, or sudden cardiac death

² Statistically significant differences between groups in event-free survival by Kaplan-Meier analysis

Table 9. Risk-Stratification Groups as Reported by Priori et al. (2003)

Risk Group	Definition	QTc	Gender	Genetic Subtype
High	≥50% likelihood of first cardiac event by age 40	≥500 msec	Any	LQT1, LQT2
		≥500 msec	Male	LQT3
Intermediate	30–49% likelihood of first cardiac event by age 40	≥500 msec	Female	LQT3
		<500 msec	Female	LQT2, LQT3
		<500 msec	Male	LQT3
Low	<30% likelihood of first cardiac event by age 40	<500 msec	Any	LQT1
		<500 msec	Male	LQT2

group with low enough risk to forego this conservative treatment. Conversely, for high-risk patients there is no evidence suggesting that genetic testing influences the decision to insert an ICD and/or otherwise intensify treatment.

6. Does genetic testing for LQTS provide information on expected response to treatment that will influence clinical decisions?

Some studies that report outcomes of treatment with beta blockers also report outcomes by specific subtype of LQTS (Schwartz et al. 2001; Priori et al. 2004). Schwartz et al. (2001) analyzed event rates by LQTS subtypes in all patients treated with beta blockers and reported that event rates were significantly lower for LQT1 subtype compared to LQT2 and LQT3. However, this analysis did not take into account pretreatment event rates, making it impossible to distinguish whether the difference is due to underlying risk of events, or differential response to beta blockers.

Priori et al. (2004) reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of beta-blocker therapy. There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss et al. (2000) also reported pre-post event rates for patients treated with beta blockers. This analysis represented a subset of patients in the larger study (139/869) with documented genotype LQT1, LQT2, or LQT3 and treatment with beta blockers. This study indicated a significant reduction in event rates for patients with LQT1 and LQT2, but not for LQT3. This analysis was also limited by the small number of patients with LQT3 and

cardiac events prior to beta-blocker treatment (4/28).

Sauer et al. (2007) evaluated differential response to beta blockers in a Cox proportional hazards analysis. These authors reported an overall risk reduction in first cardiac event of approximately 60% (HR 0.41; 95% CI: 0.27–0.64) in adults treated with beta blockers, and an interaction effect by genotype. Efficacy of beta-blocker treatment was worse in those with LQT3 genotype ($p=0.04$) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

Discussion

Overall, the evidence available to address the relevant clinical questions is not of high quality. The primary data source for the majority of studies on LQTS is the International LQTS registry. While this registry has facilitated research on LQTS by providing researchers with large amounts of data on patients with LQTS, the quality of data may often not be optimal for the research questions posed (Moss et al. 2005).

The international registry is derived from patients referred to clinical centers with an interest in LQTS, thus, creating a potential referral bias. Patients referred to these centers likely represent a more severely affected and/or complex patient group than seen in routine clinical care. There are no epidemiologic studies or studies that use patient samples representative of all patients with LQTS. In addition, the data set may not contain all of the important clinical and demographic data required to perform rigorous multivariate analysis.

The registry data is particularly weak regarding evidence on outcomes of treatment. Treatment decisions are made at the discretion of the treating physician, and there may be substantial variability in practice patterns. Where treatment outcomes are reported, there generally are a large number of patients excluded from analysis due to insufficient data. For patients with sufficient information on treatment outcomes, comparison of treatment groups are limited by the high potential for noncomparability of treatment groups.

Genetic Testing to Establish a Diagnosis of LQTS

The commercially available genetic test for LQTS is accurate in identifying a mutation that is present, and in excluding mutations that are not present. The diagnostic accuracy of genetic testing for detecting the clinical syndrome of LQTS cannot be determined with certainty due to the lack of a true gold standard for the clinical diagnosis. In patients with a known clinical diagnosis of LQTS, approximately 70% are found to have a deleterious mutation associated with LQTS, indicating that other genetic mutations may exist that have not been identified.

Of all patients found to have a genetic mutation, only a minority meet the clinical criteria for LQTS. Therefore, genetic testing will identify additional individuals with possible LQTS compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have either the pathophysiologic channelopathy associated with LQTS or the true clinical syndrome of LQTS. There is a wide variety of clinical expression in patients with the genetic defects associated with LQTS, due to incomplete penetrance and other factors. Therefore, it is possible that patients with a

genetic mutation may not ever display clinical symptoms, and that some patients may be overtreated if the diagnosis is made purely by genetic methods.

Despite the uncertainties in the diagnostic accuracy of genetic testing for clinical disease, the clinical utility of genetic testing is high. LQTS is a disorder which may lead to catastrophic outcomes, i.e., sudden cardiac death, in otherwise healthy individuals. Patients who are identified as genetic carriers of LQTS mutations have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Treatment with beta blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden death, and treatment with ICD is available for patients who fail or cannot take beta blockers. Beta-blocker treatment is a relatively low-risk, low-cost intervention that is likely to lead to large benefits in health outcomes for patients with LQTS.

Based on the available data, some conclusions can be made about the utility of genetic testing for establishing the diagnosis of LQTS. It is possible to conclude that for patients with a moderate to high pretest probability of disease, a positive test has a high positive predictive value. Table 10 demonstrates the post-test likelihood for various pretest probabilities of disease, using a sensitivity of 70% and a range of specificities. Therefore, genetic testing does have utility in confirming the diagnosis of LQTS in appropriate patient populations.

The available data also suggest that individuals identified by genetic testing should be treated in a similar fashion as patients who meet the clinical criteria for LQTS. While these patients appear to have a lower

Table 10. Post-test Likelihood of LQTS According to Pretest Probability of Disease

Pretest Likelihood of LQTS	Specificity of Genetic Testing		
	99% (LR+ = 70)	95% (LR+ = 14)	90% (LR+ = 7)
70%	>99%	97%	94%
50%	99%	93%	88%
30%	97%	86%	75%
10%	89%	61%	44%
1%	41%	12%	6.5%

LR: likelihood ratio

risk than those identified by clinical criteria, the risk of cardiac events, including sudden death, appears to be high enough to warrant treatment with lifestyle modifications and beta blockers. Furthermore, it is unlikely that the natural history of untreated patients can be evaluated more rigorously, since it will be difficult to identify a cohort of patients with LQTS who remain untreated, given the potential increased risk of mortality.

This evidence can provide some guidance on patient indications for genetic testing. Illustrative examples of patients with high, moderate, and low pretest likelihood of disease are given in the Appendix as case studies. These cases are intended to demonstrate situations where testing is definitely indicated, where uncertainty exists, and where testing is probably not indicated.

Table 11 provides one potential framework for categorizing indications for testing. The greatest utility for genetic testing will be in patients with a high pretest likelihood of LQTS, but in whom the diagnosis cannot be made by clinical criteria. The pretest likelihood of disease is dependent on whether or not there is a family history of LQTS, the length of the QT interval, and the presence of prior cardiac symptoms such as syncope. The following table is one example of how patients might be characterized by these factors in order to determine categories of patients who will and will not benefit from genetic testing.

Considerable uncertainty remains for testing in some of these patient groups. For example,

in patients with some signs or symptoms of LQTS but no family history, there may be a wide variety of clinical presentations associated with highly variable pretest likelihood of disease. For these situations, consultation with an expert in genetic testing and/or LQTS may be helpful in determining who should be tested.

If individuals who meet the clinical criteria for LQTS have immediate family members with indications for genetic testing, genetic testing of the index case can be instrumental in interpreting results of genetic testing for family members. If a known mutation is found in the index patient, then genetic testing of family members can be targeted and both positive and negative results can be interpreted with greater certainty. Therefore, the family member will benefit from genetic testing of the index patient, even if the index patient already meets the clinical criteria for LQTS.

Genetic Testing to Establish LQTS Subtype or Specific Mutation

Risk stratification in LQTS can be performed using a combination of clinical symptoms, gender, and length of the QT interval (see Case Study 4 in the Appendix). Knowledge of the specific subtype of LQTS may further assist in risk stratification. There is some evidence from registry data that prognosis differs by type of LQTS. Specifically, the Jervell and Lange Nielsen syndrome appears to have a higher risk for cardiovascular events compared with the Romano-Ward syndrome. Subtypes of the Romano-Ward syndrome may also have different prognosis. Evidence from the International LQTS registry suggests that patients with LQT1

Table 11. Potential Patient Indications for Genetic Testing

	Meets Clinical Criteria for LQTS	Some Signs or Symptoms of LQTS; Does Not Meet Clinical Criteria	No Signs or Symptoms of LQTS
Family history positive and known mutation in family	– (?)	++	+
Family history positive but family mutation status unknown	– (?)	+	+
Family history negative	–	+ (?)	–

++ definite benefit of genetic testing

+ probable benefit of genetic testing

? uncertain benefit of genetic testing

– no benefit of genetic testing

Clinical criteria for LQTS – Schwartz score ≥ 4 (other definitions possible as well)

FH positive: family history positive for sudden death at age <30; or clinical diagnosis of LQTS in family (without known mutation)

Signs/symptoms LQTS: long QT interval on EKG; syncope; aborted cardiac arrest

have a lower risk than patients with LQT2 or LQT3.

Despite the ability to risk stratify, the evidence does not permit conclusions on whether information on risk stratification leads to changes in management. It has not been possible to identify a subgroup of patients with a risk that is low enough to justify foregoing treatment with beta blockers and lifestyle modifications. Therefore, all patients with LQTS should be treated with these modalities unless contraindications exist.

Risk stratification may also potentially identify a high-risk group that should receive ICD therapy in addition to conservative management. Currently the decision to implant an ICD is based largely on the level of symptoms. Expert clinicians are likely to recommend ICD therapy in patients with documented ventricular arrhythmias, a history of sudden death, frequent syncopal episodes, and/or lack of response to conservative treatment. However, the level of absolute risk that justifies an ICD has not been explicitly defined, and the evidence does not demonstrate situations where knowledge of LQTS subtype influences the decision for an ICD. Therefore, it is difficult to determine whether knowledge of LQTS subtype will lead to information that influences clinical management.

Evidence on a differential response to treatment by LQTS subtypes is less convincing. For patients treated with beta blockers, observational data demonstrates that the rates of cardiovascular events vary among subtypes. However, these different event rates may result from different absolute risks at baseline, rather than differential response to treatment. Studies that use a pre-post design report differing results for the relative risk reduction for cardiovascular events appears to be similar among subtypes. For example, while Moss et al. (2000) report that the cardiac event rate is not reduced in a small number of patients with LQT3, Priori et al. (2004) reports a risk reduction for patients with LQT3 that is similar to other genotypes.

Summary of Application of Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments

about whether genetic testing for LQTS meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) for genetic testing for LQTS, nor are any kits being actively manufactured and marketed for distribution. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. While the FDA has technical authority to regulate home-brew tests, there is currently no active oversight nor any known plans to begin such oversight. Home-brew tests may be developed using reagents prepared in-house or, if available, commercially manufactured analyte-specific reagents (ASRs). ASRs are single biological reagents “intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens” and must meet certain FDA criteria but are not subject to premarket review.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Although there are limitations in the evidence on analytic validity, clinical validity and clinical utility, nonetheless, the overall the case that genetic testing will improve outcomes in selected patient populations is compelling. For patients with a moderate to high pretest likelihood, the positive predictive value (PPV) of genetic testing will be high, and few patients will be misclassified as having LQTS when they do not. However, for patients with a low pretest likelihood of LQTS, the PPV of testing will be lower and the utility of testing less certain.

For determining prognosis and directing therapy, the evidence is sufficient to conclude that genetic testing offers some information on risk stratification above that provided by clinical evaluation. However, genetic testing has not identified subgroups of patients with risk low enough to forego treatment, nor has

testing identified subgroups with risk high enough to justify more aggressive treatment, such as prophylactic implantation of an ICD. Similarly, while there is some evidence that certain LQTS subtypes may respond differently to beta-blocker therapy, the evidence on this is not consistent and therefore, it is not possible to conclude that genetic testing to direct therapy improves outcomes.

3. The technology must improve the net health outcome.

For patients with a moderate to high pretest likelihood of LQTS, in whom the diagnosis cannot be made after clinical evaluation, genetic testing will improve health outcomes. In these individuals, genetic testing will correctly identify patients with LQTS who cannot be diagnosed by other methods, and lead to appropriate treatment.

Patients who are identified as having LQTS by purely genetic testing have a lower risk for cardiovascular events compared to patients with a clinical diagnosis. However, the risk of cardiovascular events and sudden cardiac death in patients identified by genetic testing remains high enough to warrant treatment with lifestyle modifications and beta-blocker therapy. Observational studies show a large decrease in the incidence of cardiovascular events reported after treatment with beta blockers.

For risk stratification, the evidence is not sufficient to conclude that health outcomes are improved. Although the evidence suggests that genetic testing will aid in risk stratification, there is no evidence to suggest that testing will lead to meaningful changes in clinical management that improve health outcomes.

4. The technology must be as beneficial as any established alternatives.

The alternative to the use of genetic testing for diagnosing LQTS is using clinical methods alone for diagnosis. As discussed above, clinical methods are insensitive compared to genetic testing. When used in the correct population with a moderate-to-high pretest probability of

disease, genetic testing is more beneficial than diagnosis by clinical criteria alone.

For risk stratification, the use of genetic testing for LQTS has not been demonstrated to improve outcomes.

5. The improvement must be attainable outside the investigational settings.

At least one commercially available genetic test for LQTS is on the market, and can be ordered by any treating physician in the U.S. However, the interpretation of this test may be complex and require some expertise in genetics. Therefore, it is most appropriate that genetic testing be undertaken in clinical environments where expertise in genetic testing is available, and genetic counseling provided to patients in order to assist in complex clinical decision-making.

Based on the above, genetic testing for LQTS meets the TEC criteria for establishing the diagnosis of LQTS, in the following populations:

1. Individuals who do not meet the clinical criteria for LQTS, but who have:
 - a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation; or
 - a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable; or
 - signs and/or symptoms indicating a moderate to high pretest probability² of LQTS.
2. An individual who meets the clinical criteria for LQTS and who has a close relative at risk for LQTS with an indication for genetic testing. In this circumstance, testing of the individual with LQTS is intended to inform genetic testing options for at-risk relatives.

Genetic testing for LQTS does not meet the TEC criteria for determining prognosis and/or directing therapy in patients with known LQTS who do not have close relative(s) with indications for genetic testing.

² Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate-to-high pretest probability of LQTS is a patient with a Schwartz score of 2–5.

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Appendix

The following hypothetical case studies are intended to demonstrate the differences in expected benefit from genetic testing for different clinical situations. These are intended to be illustrative of typical situations in clinical care, but are not comprehensive and do not intend to capture all the potential manifestations of clinical situations for which genetic testing might be considered.

Case Studies: Genetic Testing to Confirm the Diagnosis of LQTS

Case 1. *Patient with a family member who has documented mutation for LQTS; patient does not meet clinical criteria for LQTS.*

This is a 32-year-old healthy female with a brother who experienced several syncopal episodes and was subsequently diagnosed with LQTS after genetic testing revealed a LQT1 mutation. The patient has a QT-interval of 440 msec, which is borderline prolonged. Her Schwartz score is 2.

This patient has a high pretest probability of LQTS of at least 50%, given that LQT1 is transmitted in an autosomal dominant fashion. Her borderline prolonged QT interval and Schwartz score indicates that her likelihood of LQTS is even higher than 50%. However, it is not possible to conclude with certainty whether LQTS is present based solely on clinical evaluation.

Without genetic testing, a clinician may choose either to treat empirically with beta blockers, or follow for any clinical symptoms (e.g., syncope) that might influence the diagnostic decision-making. If she is treated, there is a fairly high chance that she will take medications unnecessarily. On the other hand, if medications are withheld, there is a high likelihood that she will be at increased risk for sudden death.

If genetic testing is performed, it can be done in a “limited” manner, i.e., looking for the specific mutation present in her brother. While the predictive value of testing in this

situation cannot be determined with certainty, it is almost certainly high enough to influence clinical decision-making. If a mutation is present, the likelihood that she has LQTS (positive predictive value) is very high. Therefore, the diagnosis of LQTS can be made and the patient should be treated. If a mutation is absent, the likelihood that this result is a false negative is extremely low given that the analytic sensitivity of testing is greater than 99%. With a negative result on genetic testing, treatment can be appropriately withheld.

For patients similar to this, genetic testing for LQTS will improve health outcomes.

Case 2. *Patient with signs or symptoms of LQTS, but does not meet clinical criteria; family history negative for LQTS or sudden death at an early age.*

This is a 28-year-old male who presents for care after two syncopal episodes occurring in the setting of stress. He has a history of syncope as a teenager, which was attributed to vasovagal syncope. His QT-interval is 430 msec, which is borderline prolonged. His Schwartz score is 2. Initial workup for other causes of syncope is negative. There is no family history of LQTS or sudden death at an early age.

This patient has an intermediate probability of LQTS given his Schwartz score of 2, but the diagnosis cannot be made with certainty in this situation. His probability of having LQTS is lower than Case 1 due to a negative family history.

Without genetic testing, a clinician may choose either to treat empirically with beta blockers, or follow for any clinical symptoms (e.g., syncope) that might influence the diagnostic decision-making. As in Case 1, with empiric treatment there is a fairly high chance that he will either take medications unnecessarily, or be at increased risk for sudden cardiac death if medications are withheld.

“Comprehensive” genetic testing in this situation would be performed, looking for any potential mutations associated with LQTS. If testing is negative, the likelihood of LQTS is reduced, but LQTS has not been ruled out since the clinical sensitivity of genetic testing is approximately 70%. If a genetic mutation is identified, the likelihood of LQTS is increased. The precise post-test likelihood of LQTS given a positive genetic test depends on the characteristics of the identified mutation. If a mutation known to be associated with LQTS is identified (class I mutation), then the likelihood of LQTS is high. If another type of mutation is identified (class II or III), the likelihood of LQTS is less certain.

For patients similar to this, genetic testing may improve health outcomes. Testing will improve health outcomes if a class I mutation is identified. For other results, the benefit of genetic testing is unclear.

Case 3. *Patient with a borderline prolonged QT-interval identified incidentally; no other signs or symptoms of LQTS are present and family history is negative for LQTS or sudden death at an early age.*

This is a 46-year-old female scheduled for elective cholecystectomy. Her medical history is significant for hypertension and type II diabetes. Preoperative EKG reveals a prolonged QT-interval at 460 msec. Repeat EKG shows a QT-interval of 450 msec.

This patient has a low pretest probability of LQTS. Although her QT interval is slightly prolonged, it is much more likely that this represents a normal variant than LQTS. This is due to the low prevalence of LQTS in asymptomatic patients with a negative family history and the large overlap in the QT interval for patients with and without LQTS.

It is unlikely that this patient would be treated empirically for LQTS. Without treatment, there is a small chance that she will be at increased risk for sudden death or other cardiovascular symptoms.

If genetic testing is performed in this situation, “comprehensive” testing would be done. If the test is negative, the likelihood of LQTS is not changed to any significant degree. If the test is positive, the post-test probability that LQTS is present depends on

the characteristics of the identified mutation. If a known mutation is identified (class I), it is likely that LQTS is present, however, this result will probably only occur in a small number of patients with similar characteristics. For other results, the likelihood of LQTS is uncertain.

For patients similar to this, the benefit of genetic testing is unclear. While a few patients may benefit after identification of a known pathologic mutation, the overwhelming majority of patients may not, and some may be misdiagnosed with LQTS and treated unnecessarily.

Case Studies: Genetic Testing to Determine LQTS Subtype and/or Specific Mutation

Case 4. *Patient meets clinical criteria for LQTS; no known mutation in family and specific syndrome/subtype not known.*

This is a 31-year-old male undergoing work-up following an episode of near-drowning. There is a history of syncope in the past occurring in nonstressful situations, and unexplained sudden death in one male sibling at age 19. His QT-interval is 480 msec. His Schwartz score is 4.5. The diagnosis of LQTS is made and the patient is started on beta blockers. Cardiology consult is obtained and implantation of an ICD is considered.

In this situation, a Schwartz score of greater than 4 indicates that LQTS is present with a high degree of certainty. The potential value of genetic testing is in risk-stratification, and in assisting the clinician in deciding whether an ICD should be placed.

If genetic testing is negative, the patient likely still has LQTS and no information on risk stratification is obtained. If genetic testing is positive, the specific syndrome identified and/or the specific subtype may help in risk stratification. For example, if Timothy syndrome is identified (which is extremely unlikely given the lack of dysmorphic features), then the risk of sudden death is considerably higher and an ICD indicated.

However, it is more likely in this situation that Romano-Ward syndrome, and the specific subtype of Romano-Ward syndrome, will be identified by genetic testing. This information will have some value for risk

stratification, however, it is not clear the degree to which genetic testing influences risk, especially in light of other more powerful predictors such as length of QT-interval and history of cardiovascular events. Most experts will use the presence of symptoms, especially prior cardiac arrest, as the main factor in deciding whether to implant an ICD. It is not clear whether knowledge of genetic testing will influence this decision to any meaningful extent.

For patients similar to this, the benefit of genetic testing is unclear. Although genetic testing will identify the specific type of mutation in many instances, and this information will contribute to risk stratification, it is not clear that this information will affect clinical management and/or improve health outcomes.



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